REMARKS

In the Final Action dated April 1, 2009, claims 1-5, 8-34 and 37-47 are pending. Claims 28-29 are withdrawn from further consideration. Claim 37 is objected to for certain informality. Claims 1-5, 8-27, 30-34 and 37-47 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Glimcher et al. (US 2002/0059652) ("Glimcher") in view of both Shaffer et al. (*Immunity*, 2002, 17: 51-62) ("Shaffer"), Pol et al. (*J. Biomol. Screening* 2002, 7: 325-332) ("Pol"), and Mountford et al. (*Proc. Natl. Acad. Sci. USA*, 1994, 91: 4303-4307) ('Mountford").

This Response addresses the Examiner's rejection and objection. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

Claim Amendments

Claims 20 and 22 have been amended to clarify claim language. Claim 37 has been amended to address a formality objection. No new matter is introduced.

Formality Objection

In light of the amendment to claim 37, the objection thereof is obviated and withdrawal of the objection is therefore respectfully requested.

35 U.S.C. §103(a)

Claims 1-5, 8-27, 30-34 and 37-47 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Glimcher in view of Shaffer, Pol, and Mountford.

Examiner's Reasoning

Glimcher teaches a transgenic mouse comprising a modified *xbp-1* gene encoding functional or non-functional XBP-1 polypeptide co-expressed with a selectable marker or GFP. Glimcher also teaches using the transgenic mouse or B- or T-cells obtained from the mouse to screen for agonists or antagonists of terminal differentiation of B- or T-cells, wherein the test compound modulates the activity of the XBP-1 polypeptide in the B- or T-cells. Glimcher does not teach genetically altering the *Blimp-1* gene or screening for compounds capable of modulating Blimp-1 activity. However, the Examiner notes that the reference teaches that XBP-1 acts downstream of Blimp-1. Additionally, Shaffer allegedly teaches that Blimp-1 is the master regulator of plasma cells terminal differentiation, wherein Blimp-1 acts by allowing the expression of specific transcription factors such as XBP-1. Therefore, the Examiner concludes that it would have been obvious to one of skill in the art, at the time the invention was made, to modify the cells and method of Glimcher by substituting XBP-1 with Blimp-1 to achieve the predictable result of screening for agonists or antagonists of terminal differentiation of B- or T-cells.

The Examiner admits that Glimcher et al. and Schaffer et al. do not teach inserting a nucleic acid encoding a reporter molecule into an intron of the *Blimp* locus to obtain a modified *blimp* allele comprising the Blimp coding sequence and the reporter under the control of the endogenous *Blimp* regulatory elements (claims 1-3 and 30-32). However, the Examiner alleges that Pol supplies such teaching. Pol allegedly suggests using homologous recombination to place a reporter such as GFP under the control of the endogenous regulatory elements of a gene of interest, wherein the detection of the reporter indicates a cellular phenotype. Further, the Examiner points out that at the time the invention was made, homologous recombination to

obtain cells comprising homozygous or heterozygous modifications was routine in the prior art. For example, Mountford teaches using homologous recombination in ES cells to place reporters under the control of regulatory sequences of endogenous genes of interest with or without modifying the endogenous gene, wherein insertion could be within an exon or within an intron.

Therefore, the Examiner concludes that it would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Glimcher and Shaffer, by using homologous recombination to place GFP into an intron of the *Blimp* allele to achieve the predictable result of obtaining a genetically modified cell suitable for high-throughput screening of test agents capable of modulating the Blimp-1 activity. According to the Examiner, by going so, one of skill in the art would have used a targeting vector as recited in instant claims 44-47, and would also have practiced a method of monitoring a B or T-cell, wherein detection of the reporter indicates the commitment of the B or T-cell to terminally differentiate (as in instant claims 20-27).

Applicants respectfully disagree. Specifically, as further discussed herein below and as supported by the §1.132 Declaration of Dr. Nutt (attached), the Examiner's rationale underlying his conclusion that it would have been obvious to modify the cells and method of Glimcher by substituting XBP-1 with Blimp-1 is flawed. Further, the Examiner's combination of the references is improper. Moreover, even assuming that the teachings of the references were to be combined, the results achieved by the present invention were still unexpected to those skilled in the art.

XBP-1 not necessarily downstream of Blimp-1

The Examiner's premise for concluding the obviousness of modifying the cells and method of Glimcher by substituting XBP-1 with Blimp-1 is that XBP-1 allegedly acts

downstream of Blimp-1. The Examiner refers to [0214]-[0215] of Glimcher and to Shaffer in support of the notion that XBP-1 acts downstream of Blimp-1.

However, Applicants respectfully submit that the Examiner's premise that XBP-1 acts downstream of Blimp-1 is incorrect. Applicants respectfully direct the Examiner's attention to the Declaration, paragraphs 4-5, where Dr. Nutt testified that based on a careful reading of Glimcher and Shaffer, and other references available at the relevant time, it was not possible for one skilled in the art to conclude that XBP-1 acts specifically downstream of Blimp-1. In fact, XBP-1 has been shown to be expressed both upstream and downstream of Blimp-1.

Combination of References Improper

Applicants observe that the genetically modified cells disclosed by Glimcher include animals/cells which lack XBP-1 (abstract and paragraphs [0004], [0011], [0083], [0091], [0178] and [0214]), have over-expressed XBP-1 in conjunction with a reporter gene responsive to the XBP-1 protein (paragraphs [0006] and [0214]), have over-expressed XBP-1 (paragraphs [0031], [0053], [0068] and [0073]), have an XBP-1 transgene driven by a liver-specific promoter (paragraph [0011]), or have an altered XBP-1 (paragraph [0082]). Applicants respectfully submit that modifying the cells and methods of Glimcher, as suggested by the Examiner, would result in the generation of a knockout Blimp mouse or cells lacking Blimp-1. See the abstract and paragraphs [0004], [0011], [0083], [0091], [0178] & [0214] of Glimcher). Alternatively, one would obtain (1) cells which over-express Blimp-1 in conjunction with a reporter gene responsive to the Blimp-1 protein (paragraphs [0006] and [0214]); (2) cells which over-express Blimp-1 (paragraphs [0031], [0053], [0068] and [0073]); (3) cells which have a *Blimp-1* transgene driven by a liver-specific promoter (paragraph [0011]), or (4) cells which have an altered Blimp-1 (paragraph [0082]) in contrast to wild type Blimp-1. However, none of these

alternatives would provide a cell or non-human organism comprising such a cell containing a genetic modification characterized by the insertion of a reported gene in an endogenous *Blimp-1* allele, as presently claimed.

Importantly, there is no disclosure or suggestion in Glimcher of a modified *Blimp* gene being endogenous *Blimp* inserted with a reporter driven by endogenous *Blimp* regulatory elements, as presently claimed. The Examiner has attempted to rely on Pol and Mountford to cure this fundamental deficiency of Glimcher, because Pol allegedly teaches placing a reporter under control of the endogenous regulatory elements of a gene of interest wherein the detection of the reporter indicates a cellular phenotype, and Mountford allegedly teaches the relevant methodology to do so.

However, Applicants respectfully submit that the premise for Pol's placement of a reporter under control of the endogenous regulatory elements of a gene of interest was that the genes of interest had already been identified to be specifically expressed in lesional psoriatic skin, but normal skin; i.e., expression of these genes was a surrogate marker for psoriasis. In the present case, absent the recognition that terminal differentiation of cells is linked to expression of Blimp-1, which is provided uniquely by the present invention, those skilled in the art would not have been motivated to rely on Pol and place a reporter gene under control of endogenous *Blimp* regulatory elements. Applicants respectfully submit that the Examiner has engaged in impermissible hindsight construction by combining the teachings of Glimcher with Pol and Mountford.

The results achieved by the claimed invention are unexpected.

The Examiner contends that by modifying the cells and method of Glimcher via substituting XBP-1 with Blimp-1, it would have been obvious to one of skill in the art, at the

time the invention was made, to achieve the predictable result of screening for agonists or antagonists of terminal differentiation of B- or T-cells.

Applicants respectfully disagree and direct the Examiner's attention to the Nutt Declaration (paragraphs 6-8).

As Dr. Nutt testified (paragraph 6), prior to the present invention, there were no good markers in the art for fully differentiated antibody secreting cells ("ASCs" or plasma cells). It has been a unique recognition provided by the present invention that not only substantially all ASCs express Blimp-1 in a cell population, but also no pre-plasma/ASC cells express Blimp-1. See pages 65-67 (Examples 3-4) of the specification. Similar expression profiles were also observed with terminally differentiated T cells although expression of Blimp-1 was at a lower level.

As Dr. Nutt further explained (paragraph 7), the specific association of the expression of Blimp in plasma cells – i.e., expression in *all* plasma cells and lack of expression in earlier stages of B and T-cell differentiation, makes Blimp an especially useful marker for identifying modulators of terminal differentiation. In contrast, *XBP-1* is expressed upstream and downstream of signals that drive plasma cell differentiation (see the Nutt Declaration). Therefore, identifying modulators of endogenous *XBP-1* expression would not appear to provide a selective method for screening for modulators of terminal differentiation. Furthermore, if only a proportion of cells endogenously express XBP-1 and only for some time, it would be more difficult to identify modulators of endogenous expression.

In paragraph 8, Dr. Nutt testified that prior to the present invention, targeting of *Blimp* was considered to potentially suffer from the same problems. It was not known and could not have been predicted that *all* fully differentiated antibody secreting cells (ASCs or plasma

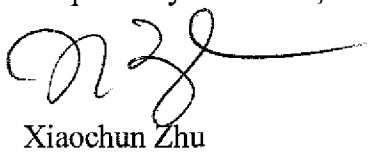
cells) express Blimp-1. It is evident that Blimp's endogenous expression consistently and only in terminal differentiated haematopoietic cells makes the claimed assays, and the related cells and vectors, much more improved over the XBP-1 based methodology disclosed by Glimcher. The results achieved by the present invention are not only superior but also unexpected to those skilled in the art.

Conclusion

Applicants respectfully submit that Glimcher does not teach or suggest the claimed invention, and does not provide a motivation, alone or in combination with Pol and Mountford, for those skilled in the art to achieve the claimed invention. Further, even if, *pro arguendo,* the skilled person did use those cells and methods of Glimcher and substituted XBP-1 with Blimp-1, the results achieved by the present invention were still beyond the reasonable expectation of those skilled in the art. Therefore, it is respectfully submitted that the claimed invention is not obvious in view of the combination of Glimcher, Shaffer, Pol and Mountford. Withdrawal of the rejection under 35 U.S.C. §103(a) is therefore respectfully requested.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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